REMARKS/ARGUMENTS

Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 are under consideration in the instant application.

Claims 26, 27, 34, 37, 40 and 44 have been amended.

Claims 58 and 59 are new.

EXAMINER INTERVIEW

Applicant thanks Examiners Nissa Westerberg and Humera Sheikh for the meeting with Applicant's agent, D'vorah Graeser, on September 10 2008 in which the rejections of the claims in the Office Action of June 23 2008 were discussed, as was the cited art. Proposed claim amendments and additional claims were discussed. Applicant thanks the Examiners for their time and consideration.

Rejections Under 35 U.S.C. §112

The Examiner has rejected claims 34, 37, 40, and 44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states that claim 37 is rejected since it is unclear what grade(s) of lactose are encompassed by the limitation "a suitable grade of lactose" and/or what properties of lactose would cause it to be of an unsuitable grade.

Claim 37 has been amended to clarify that the filler is lactose monohydrate, as supported by the specification at paragraph 0017, last two lines, which states that fillers such as lactose monohydrate may be used.

The Examiner states that claim 40 is rejected due to the use of the phrase "at least one of sodium stearate", which concludes the claim. The Examiner considers that it is unclear whether the Applicant wished to name other organic basic salts, since the term

"at least one of" generally introduces a Markush group, but the list of items to be chosen is only one.

The Applicant has amended claim 40 to recite "comprises sodium stearate" to clarify that no other organic base salts are specifically named, as supported by the specification at paragraph 0019, which refers to the organic basic salt as including but not limited to sodium stearate.

The Examiner states that claim 44 is rejected due to the use of the limitation "said active coating" in lines 1-2, which has insufficient antecedent basis in claim 27. Claim 44 has been amended to replace the term "active coating" with the term "subcoating layer", as supported by the specification at paragraph 0053, and for which antecedent basis is found in claim 27.

The Examiner further states that it is unclear how claims 44 and 34 differ, as both require the active coating to comprise at least one surfactant selected from the group consisting of Tween®80 and sodium lauryl sulfate. Amended claim 44 refers to the surfactant as being present in the subcoating layer rather than in the active coating.

The Examiner further states that claims 34 and 44 are rejected due to the use of the trademark/trade name Tween®80. The trademark/trade name has been replaced with the term polysorbate 80.

Rejections Under 35 U.S.C. §102

The Examiner has rejected claims 27-32, 38, 39, 42, 46, 47, 49 and 50 under 35 U.S.C, 102, second paragraph, as being anticipated by Depui et al (WO 96/24375).

As recited in claims 26 and 27, the characterizing feature of the substrate of the present invention is that the substrate does not include an alkaline agent. As stated on page 13, lines 28-30 of WO '375, the core may optionally comprise an alkaline substance together with the proton pump inhibitor. Hence, the absence of an alkaline compound in the core is clearly not a characterizing feature of the formulation of WO '375.

Although the use of an alkaline agent in the separating layer is stated as being optional (page 14, last paragraph, bridging page 15), there is no specific teaching of a

composition comprising lansoprazole which is devoid of an alkaline agent in the core and includes an alkaline agent in the separating layer. Furthermore, as stated on page 16, first paragraph, a separating layer is not essential for the invention.

The Examiner states that Examples 8 (beginning of page 28) and 11 (beginning of page 39) of WO '375 teaches a multilayer dosage form comprising lansoprazole in the free base form. The core contains a sugar sphere seed coated with lansoprazole, HPMC and water. No alkaline material is present in the core. The separating layer comprises HPMC, talc as filler, magnesium stearate as alkaline agent, and water as the solvent. An enteric coating layer comprising a methacrylic acid and the plasticizer triethyl citrate is present in the dosage form.

The Applicant respectfully wishes to point out that Example 8 begins on page 34 and refers to an enteric coating layered tablet which does not include a neutral core. The Applicant therefore assumes that the reference is to Example 5, beginning on page 28, which comprises sugar sphere seeds.

Example 11 teaches a capsule formulation comprising omeprazole. The capsules comprise pellets having a composition as described in Example 1.

Examples 5 and 11 include magnesium stearate in the subcoating layer, which the Examiner refers to as an alkaline agent. However, the specification of WO '375 refers to magnesium stearate as an example of an additive such as a plasticizer, colorant, pigment, filler, antitacking agent and antistatic agent (page 15, lines 12-15), and does not include this compound in the list of possible alkaline agents on page 14, third paragraph. As shown in the attached pages from Pharmaceutical Excipients, (London: Pharmaceutical Press. Electronic version, 2006), magnesium stearate is practically insoluble in ethanol, ether and water. The separating layer of Example 5 is prepared in water. An alkaline agent is, by definition, soluble in water, hence insoluble magnesium stearate cannot be considered an alkali agent. In contrast, the formulation of the present invention uses soluble sodium stearate in the subcoating layer, which is effective as an alkalinizing agent.

Hence, WO '375 does not teach use of an alkaline agent in the subcoating layer, and therefore does not destroy novelty of independent claim 27, or claims 28-32, 38, 42, 46, 47, 49 and 50 depending directly or indirectly therefrom.

Furthermore, with regard to Example 5, the active ingredient is omeprazole, whereas claim 27 specifically recites lansoprazole. The two drugs are not in fact interchangeable and have different properties in formulations.

Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 27-32, 36-39, 42, 46, 47, 49 and 50 under 35 U.S.C, 103, first paragraph, as being unpatentable over Depui et al (WO 96/24375).

The Examiner states that WO '375 discloses an oral, enteric coated dosage form comprising an acid labile proton pump inhibitor useful in the treatment of disorders associated with *Heliobacter* infections (abstract). According to the Examiner, in Examples 8 (beginning page 28) and 11 (beginning on page 39), a multilayer dosage form comprising lansoprazole (in the free base form) is prepared. The Examiner states that Examples 8 (beginning of page 28) and 11 (beginning of page 39) of WO '375 teaches a multilayer dosage form comprising lansoprazole in the free base form. The core contains a sugar sphere seed coated with lansoprazole, HPMC and water. No alkaline material is present in the core. The separating layer comprises HPHC, talc as filler, magnesium stearate as alkaline agent, and water as the solvent. An enteric coating layer comprising a methacrylic acid and the plasticizer triethyl citrate is present in the dosage form. The active ingredient can be mixed with other ingredients such as binders, surfactants and fillers. In Example 18, the surfactant sodium lauryl sulfate and the filler anhydrous lactose are included in the same layer as the active ingredient (omeprazole).

The Examiner considers that WO '375 differs from the instant invention only in that a surfactant such as sodium lauryl sulfate and the filler lactose are present in the same layer as the active ingredient, and that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare such a formulation as WO '375 discloses such a formulation using the functionally equivalent therapeutic agent omeprazole.

As discussed above with regard to novelty, magnesium stearate is not disclosed in WO '375 as being suitable for use as an alkaline agent in the separating layer, but is rather described as an additive such as a plasticizer, colorant, pigment, filler, antitacking agent and antistatic agent. Hence, WO '375 does not teach a formulation which differs from that of the present invention only in that a surfactant such as sodium lauryl sulfate and filler lactose are used. The use of a subcoating layer comprising an alkaline agent is neither taught nor suggested by WO '375.

The Applicant therefore believes that independent claim 27, and claims 28-32, 38, 42, 46, 47, 49 and 50 depending directly or indirectly therefrom are not rendered obvious by the teachings of WO'375.

The Examiner further states that claims 26-32, 34, 36-39, 42, 46, 47, 49, and 50 are unpatentable over WO '375 in view of Lundberg et al. (EP 1174136).

According to the Examiner, WO '375 discloses a multilayer oral lansoprazole formulation in which the subcoating layer comprises a cellulosic polymer, filler, alkaline agent and a solvent. WO '375 does not disclose the inclusion of a surfactant in the subcoating layer. Lundberg et al. discloses similar trilayer (active ingredient core, intermediate layer and enteric layer). In Example 1, a separating layer comprises talc (filler), sodium dodecyl sulfate (surfactant), microcrystalline cellulose (cellulosic polymer) and magnesium stearate (alkaline agent). The Examiner therefore considers that it would have been obvious to one of ordinary skill in the art at the time of the instant invention to include a surfactant in the subcoating layer taught by Lundberg et al as a suitable composition for an intermediate layer in trilayer proton pump inhibitor dosage forms.

As discussed above, the instant invention comprises an alkaline agent in the subcoating layer. As further discussed above, magnesium stearate cannot be considered an alkaline agent. Hence, neither WO '375 nor Lundberg et al, either alone or in combination, teach or suggest a composition for a PPI which includes an intermediate layer comprising an alkaline agent.

The Applicant therefore believes that independent claims 26 and 27, and claims 28-32, 38, 42, 46, 47, 49 and 50 depending directly or indirectly therefrom are not rendered obvious by the teachings of WO'375 in view of Lundberg et al.

The Examiner has stated that the Applicant has not defined what additional components in the subcoating layer defined in claim 26 would materially affect the basic and novel characteristics of the invention.

The use of the term 'consisting essentially of' is intended to exclude all other components, such as, for example, additional active ingredients, which would add to the cost and complexity of manufacture of the composition of the instant invention.

The Examiner has rejected claims 27-32, 34, 36-40, 42, 46, 47, 49 and 50 as being unpatentable over WO '375 in view of Edgren et al (U.S. 6,210,712).

The Examiner states that WO '375 does not disclose the inclusion of sodium stearate in the subcoating layer. The Examiner further states that Edgren et al discloses that potassium stearate, magnesium stearate and sodium stearate are functionally equivalent. The description at column 8, lines 6-10 of Edgren et al describes the use of such stearate salts as lubricants, and not as alkaline agents. The present invention uses sodium stearate as an alkaline agent and not as a lubricant. Also sodium stearate is known to be weaker than magnesium stearate, while both alkaline agents are weak alkaline agents, such that using the weakest member of an already weak group of alkaline agents would not be expected to have the desired effect on preserving the stability of the formulation overall and of lansoprazole in particular. As discussed above, magnesiuum stearate for use as an excipient such as a plasticizer is known, however magnesium stearate cannot be considered an alkaline agent. Hence, magnesium stearate is not functionally equivalent to sodium stearate in the context of the present invention.

Furthermore, claim 26 now recites polysorbate 80 and sodium lauryl sulfate as the specific surfactants, which are particularly useful for the present invention. The use of these specific surfactants in the subcoating layer is not taught or suggested by any of the cited references. Claim 26 also recites specific cellulosic polymers, namely hydroxypropyl methylcellulose (HPMC), ethylcellulose and hydroxypropyl cellulose (HPC), or a mixture thereof; the combination of such specific cellulosic polymers,

surfactants and alkaline agent was not taught or suggested by any of the references, alone or in combination.

Hence, WO '375 in combination with Edgren et al, do not teach or suggest the method of the present invention. The Applicant therefore believes claims 27-32, 34, 36-40, 42, 46, 47, 49 and 50 to be non-obvious over WO '375 in view of Engren et al.

The Examiner has rejected claims 27-32, 34, 36-39, 41, 42, 46, 47, 49 and 50 as being obvious over WO '375 in view of Depui et at (US 2002/0155153).

The Examiner states that WO '375 does not disclose the inclusion of an inorganic base salt in the subcoating layer or Tween®80 or sodium lauryl sulfate in the active ingredient layer. US '153 discloses that the optional separating layer, between the core containing the proton pump inhibitor active ingredient and the enteric coating layer can contain pH buffering agents such as the inorganic salts generally used as antacids.

The Examiner therefore considers that it would have been obvious to one of ordinary skill to replace the alkaline magnesium stearate in the subcoating layer of the dosage form of WO '375 with an inorganic base salt, taught by US '153 as suitable alkaline agents that improve the pH buffering capacity of the subcoating layer.

As discussed above, WO '375 does not disclose a formulation comprising lansoprazole which includes an alkaline agent in the subcoating layer. There would therefore have been no motivation for one of ordinary skill in the art to include an inorganic base salt as taught by US '153 in a formulation as taught by WO '375, which is devoid of an alkaline agent.

The Applicant therefore believes claims 27-32, 34, 36-39, 41, 42, 46, 47, 49 and 50 to be non-obvious over WO '375 in view of US '153.

The Examiner has rejected claims 26-32, 34, 36, 38, 39, 41, 42, 46, 47, 49 and 50 as being obvious over Depui et al (US 2002/0155153).

The Examiner states that although US '153 does not explicitly disclose a lansoprazole preparation in which an inorganic or organic base salt is present in the separating layer, it would have been obvious to one of ordinary skill in the art to prepare a multilayer lansoprazole oral dosage for administration as taught by US '153, and to

include an alkaline agent in the separating layer, as the inclusion of such compounds in the separating layer is taught to improve the pH buffering capacity of this layer.

US '153 teaches pharmaceutical preparations comprising a proton pump inhibitor in combination with one or more NSAID(s), wherein at least the proton pump inhibitor is protected by an enteric coating.

Paragraphs 0047 and 0057 teach that the proton pump inhibitor may be provided in the form of the alkaline salt, or optionally combined with alkaline reacting substances. The composition of US '153 is clearly not characterized by the absence of an alkaline agent in the substrate.

Example 4, as referred to by the Examiner, discloses enteric coated lansoprazole pellets. The subcoating layer does not include an alkaline agent. The lansoprazole containing pellets are compressed on top of naxopren-containing granules to provide a two layered tablet. This is an entirely different formulation to that of the present invention. The disclosure of US '153 provides no motivation to include an alkaline agent in the subcoating layer of the two layered tablet of Example 4, since, as stated in paragraph 0021, the enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units, and provides a good stability during long-term storage.

Claims 26 and 27 have been amended to specify that lansoprazole is the sole active ingredient in the composition of the instant invention. Support for this amendment is found throughout the specification, such as in Exanple 1.

The Applicant therefore believes that claims 26-32, 34, 36, 38, 39, 41, 42, 46, 47, 49 and 50 are non-obvious over US '153.

The Examiner has rejected claims 26-32, 34, 36, 38, 39, 41, 42, 44, 46, 47, 49, and 50 as being obvious over US '153 in view of Lundberg et al.

US '153 does not disclose the inclusion of a Tween®80 or sodium lauryl sulfate in the subcoating layer. Lundberg teaches surfactants such as sodium lauryl sulfate or polysorbates.

The Examiner states that it would have been obvious to one of ordinary skill to include sodium lauryl sulfate or a polysorbate, as taught by Lundberg et al as being functionally equivalent to PEG 6000 present in the subcoating layer of the dosage form taught by US '153.

As discussed above, US '153 does not disclose a dosage form comprising lansoprazole, in which the subcoating layer comprises an alkaline agent and the substrate does not include an alkaline agent. Hence, the substitution of the surfactants described by Lundberg et al for those disclosed in US '153 would not result in the formulation of the instant invention.

The Applicant therefore believes that claims 26-32, 34, 36, 38, 39, 41, 42, 44, 46, 47, 49, and 50 are non-obvious over US '153 in view of Lundberg et al.

The Examiner has rejected claims 26-32, 34, 36, 38-42, 46, 47, 49 and 50 as being obvious over US '153 in view of Edgren et al. The Examiner states that US '153 does not disclose the inclusion of sodium stearate in the subcoating layer. Edgren et al discloses potassium stearate, magnesium stearate and sodium stearate as being functionally equivalent.

As discussed above, US '153 does not disclose a dosage form comprising lansoprazole, in which the subcoating layer comprises an alkaline agent and the substrate does not include an alkaline agent. Magnesium stearate is disclosed in paragraph 0061 as an example of an additive such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents. Use of magnesium stearate as an alkaline agent is neither taught nor suggested. Furthermore, as discussed above, Edgren discloses magnesium stearate and sodium stearate as being functionally equivalent as plasticizers, and not as alkaline agents.

Hence, US '153 and Edgren et al do not teach or suggest, either alone or in combination, the method of the instant invention.

The Applicant therefore believes claims 26-32, 34, 36, 38-42, 46, 47, 49 and 50 to be non-obvious over US '153 in view of Edgren et al.

The Examiner has rejected claims 26-32, 34, 36-39, 41, 42, 44, 46, 47, 49 and 50 as obvious over US '153 in view of WO '375.

US '153 does not disclose the inclusion of the filler lactose in the active coating. WO '375 discloses a pharmaceutical composition of omeprazole in which the portio of the dosage form with the active ingredient includes the filler lactose. The Examiner therefore considers that it would have been obvious to one of ordinary skill in the art to prepare a multilayer lansoprazole dosage form as taught in US '153 and to include a lactose filler in the active coating as taught in WO '375.

As discussed above, US '153 does not disclose a dosage form comprising lansoprazole, in which the subcoating layer comprises an alkaline agent and the substrate does not include an alkaline agent. Hence, use of lactose in the active coating would not result in the formulation of the instant invention.

Claims 58 and 59 further encompass previously presented limitations of previously presented claims, and overcome the cited art for the reasons given above.

The present response is intended to be fully responsive to all points of objection raised by the Examiner and is believed to place claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 in condition for allowance. Favorable reconsideration and allowance of the pending claims is respectfully requested.

Should any questions remain unresolved, the Examiner is requested to telephone Applicants' Agent.

Respectfully submitted,

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